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Pharmacology, Biochemistry and Behavior 71 (2002) 325–332

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

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Acute locomotor effects of fluoxetine, sertraline, and nomifensine in young versus aged Fischer 344 rats

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Received 8 May 2001; received in revised form 11 September 2001; accepted 15 September 2001

Abstract

Spontaneous locomotor activity was measured in young (6–8 months) and aged (24–26 months) Fischer 344 (F344) rats. Following habituation to the activity monitors, aged rats demonstrated significantly diminished motor activity as quantified by total distance traveled and vertical activity. Movement speed did not differ significantly between the two groups. Following habituation, rats were administered acute doses of fluoxetine, sertraline, or nomifensine (1.0, 3.0, and 10.0 mg/kg). Fluoxetine diminished all three behavioral measures in the young rats, while in the old rats, fluoxetine's effects were limited to a robust attenuation of vertical activity. Sertraline decreased movement speed and vertical activity, but not total distance traveled, in the young rats. Unlike fluoxetine, sertraline produced no significant effects on any of the three behavioral variables in the old rats. Nomifensine increased behavioral scores for both age groups. The results are discussed in relation to acute motor side effects of selective serotonin reuptake inhibitors (SSRIs) in motor-impaired aged individuals, as these effects may influence their eventual use in the clinic.

Keywords: Aging; Locomotor activity; Dopamine; Serotonin; Transporters; Antidepressants; SSRI

1. Introduction

In humans and in animals, old age is often associated with a marked deterioration of motor function. Age-related motor decrements include akinesia (or bradykinesia), rigidity, gait and postural disturbances, and tremor (Bennett et al., 1996; Mortimer and Webster, 1982; Teräväinen and Calne, 1983). The fact that these decrements are also the cardinal symptoms of Parkinson's disease (PD) suggests that neuronal dopamine (DA) systems may be adversely affected by advancing age. This hypothesis is supported by reports of diminished function in the nigrostriatal DA system in aged humans and animals (e.g., Carlsson and Winblad, 1976; Emborg et al., 1998; Emerich et al., 1993; Fearnley and Lees, 1991; Hebert and Gerhardt, 1998; McGeer et al., 1977).

Previous studies have reported that in the laboratory, rats and monkeys display progressive age-related attenuations in spontaneous motor activity that are analogous to the akinesia observed in elderly humans (Emborg et al., 1998; Emerich et al., 1993; Hebert and Gerhardt, 1998; Willig et al., 1987). The fact that drugs that inhibit DA uptake, such as GBR 12909 and nomifensine, have been found to reverse motor impairments in aged rats and monkeys (Grondin et al., 2000; Hebert and Gerhardt, 1998) suggests that they may have therapeutic utility in the treatment of age-related akinesia. Moreover, because of the substantial comorbidity between age-related motor deficits and depressive symptomatology (Bennett et al., 1996), DA uptake-inhibiting drugs with antidepressant properties would be of particular interest. One problem with this strategy, however, is that the therapeutic effects of most antidepressant drugs are achieved by increasing central serotonergic transmission, which has been reported to

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0091-3057/01/$ – see front matter
PII: S0091-3057(01)00655-4

produce acute hypodopaminergic effects in subcortical regions of the basal ganglia (Di Mascio et al., 1998; Gerson and Baldessarini, 1980; Prisco and Exposito, 1995). These effects could exacerbate the already diminished motor function in the elderly patient and, consequently, affect compliance (Gareri et al., 2000).

The purpose of the present study was to measure the acute effects of three antidepressant drugs — fluoxetine, sertraline, and nomifensine — with varying degrees of DA uptake inhibiting properties on spontaneous locomotor activity in young versus old Fischer 344 (F344) rats. Despite the fact that sertraline and fluoxetine are both classified as selective serotonin reuptake inhibitors (SSRIs), their pharmacological profiles are unique. While both are effective inhibitors of serotonin (5-HT) uptake, the in vitro potency of sertraline is over 35 times greater than that of fluoxetine. Unlike fluoxetine, however, sertraline also demonstrates relatively strong DA uptake inhibiting properties (Bolden-Watson and Richelson, 1993; Hyttel, 1993; Richelson, 1994; Tatsumi et al., 1997). In fact, in one study investigating the potencies for 37 antidepressants for human DA, 5-HT, and norepinephrine transporters, only two compounds, sertraline and nomifensine, were found to exhibit appreciable potencies for the DA transporter, with sertraline's potency being over twice that of nomifensine (Tatsumi et al., 1997). Nomifensine's effects at the 5-HT transporter were negligible.

Although the acute effects of fluoxetine and sertraline on locomotor activity have been previously tested in young adult rats, there are, to our knowledge, no published reports describing the acute effects of these drugs on spontaneous motor activity in aged animals. Generally, acute administration of fluoxetine and sertraline either decreases or does not affect spontaneous motor activity in young rats (Koe et al., 1983; Maj et al., 1996; Sills et al., 1999), effects that may be related to transient decreases in DA function in the basal ganglia (Clark et al., 1996; Dewey et al., 1995; Ichikawa and Meltzer, 1995). However, there is evidence that repeated administration of these drugs may result in increased DA function in the basal ganglia (Collu et al., 1997; Kennett et al., 1994). However, since SSRIs generally require several weeks to achieve therapeutic efficacy (Goodnick and Goldstein, 1998), studies comparing the acute effects of these drugs on motor function between normal young animals and motor-impaired old animals should yield valuable information that may influence their eventual use in the clinic. Although nomifensine is not a commercially available antidepressant, its effects as a DA uptake inhibitor with negligible potency for the 5-HT transporter were measured for comparative purposes. By administering the same doses of each drug to each animal (as opposed to a between-groups chronic dosing design incorporating the same range of doses), a more comprehensive study of the acute effects of these drugs can be accomplished with fewer rats while providing a foundation for future chronic studies.

2. Materials and methods

2.1. Subjects

Male F344 young adult (6 months; $n = 10$) and aged (24 months; $n = 10$) rats were obtained from the NIA colonies. Animals were housed in laminar flow units with ad libitum access to food and water. The body weights of the animals averaged 329 ± 9 g for the young rats and 406 ± 10 g for the old rats on the first day of habituation. Animals had no previous drug exposure and protocols were approved by the local Institutional Animal Care and Use Committee.

2.2. Drugs

Fluoxetine hydrochloride and nomifensine maleate (Research Biochemicals International, Natick, MA) was dissolved in physiological saline solution. Sertraline (generously provided by Pfizer, Groton, CT) was dissolved in a 5% alkamuls (formerly Emulpher; Rodia, Cranbury, NJ)/5% ethanol/90% saline solution.

2.3. Apparatus

Locomotor activity was assessed during the light period using four automated activity chambers (Model RXYZCM-8, Accuscan Instruments, Columbus, OH). Each monitor consisted of a $41 \times 41 \times 31$-cm^3 Plexiglas box with a grid of infrared beams mounted horizontally every 2.5 cm and vertically every 4.5 cm. The monitors were connected to a Digiscan Analyzer (Model DCM-8, Accuscan Instruments) that transmitted the number of beam breaks (activity data) to a computer. During operation, the pattern of beam interruptions was recorded and analyzed by the computer. Activity data were collected during six consecutive 10-min periods.

2.4. Procedure

2.4.1. Behavioral measures

Prior to drug administration, animals were allowed to habituate to the locomotor activity monitors during 10 daily 60-min sessions. Three measures of overall locomotor activity were ascertained during the behavioral sessions: total distance traveled, average movement speed, and vertical activity. Total distance traveled was quantified as the sum of the distance measures (in centimeters) across the six 10-min samples. Average movement speed was calculated by dividing the total distance traveled by total movement time (in seconds). Vertical activity was quantified as the sum of the number of vertical photobeam interruptions across the six 10-min samples.

2.4.2. Drug administration

Animals were administered fluoxetine, sertraline, or nomifensine (1, 3, and 10 mg/kg ip) on every fourth day,

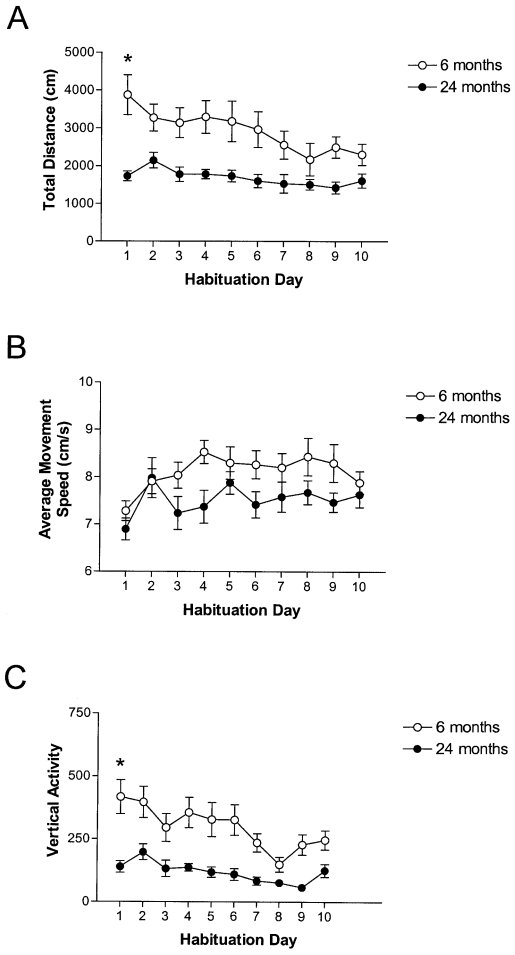

Fig. 1. Habituation of locomotor activity measures in young versus aged F344 rats. (A) From the first day of habituation (* $P<.05$), total distance traveled was significantly lower in the old rats than in the young rats. Total distance traveled decreased from Day 1 to Day 10. (B) Average movement speed, which did not differ between the two age groups, increased from Day 1 to Day 10. (C) Vertical activity, which was also lower in the old rats from the first day of habituation (* $P<.05$), decreased from Day 1 to Day 10.

with all animals receiving each dose of the three drugs via a randomized schedule. The three drugs were administered concurrently. The doses used in the current study were selected based on previous studies of fluoxetine and sertraline in young animals (Maj et al., 1996; Sills et al., 1999) and nomifensine in young and aged animals (Hebert and Gerhardt, 1998). Drugs were administered 30-min prior to animals' placement into the activity monitors. On the days immediately preceding drug administration days, vehicle data (either saline or the alkamuls/ethanol/saline solution, depending on the drug scheduled to be administered the following day) were collected. The two age groups were tested concurrently.

2.4.3. Data analysis

All statistical analyses were conducted on raw data. To examine age-related differences in the behavioral measures during habituation, two-way analyses of variance (ANOVAs) with age as the between-subjects factor and day of habituation as the within-subjects (repeating) factor were conducted for each dependent variable. Prior to analyses of drug effects, baseline differences between the two age groups were analyzed using independent samples' t tests for each dependent variable. Baseline values were means for all vehicle injection days for each dependent variable. Because of robust between-groups differences in baseline values, effects for each drug were analyzed independently for each age group using a repeated-measures ANOVA with dose as the repeated-measures factor. Post hoc tests were conducted to determine which doses differed significantly from vehicle values. All differences tested post hoc were considered significant at $P<.05$ following Bonferroni's correction for multiple tests.

3. Results

3.1. Habituation

From the first day of habituation, total distance traveled [main effect for age: $F(1,18)=14.5711$, $P=.001$; post hoc means test day 1: $P<.05$] and vertical activity [main effect for age: $F(1,18)=28.9915$, $P<.0001$; post hoc means test day 1: $P<.05$] were significantly lower in the old rats than in the young rats (see Fig. 1). Movement speed did not differ significantly between the two age groups. While ANOVAs revealed a significant main effect for day during habituation (scores decreased from the first day) for total distance traveled [$F(9,162)=4.2329$, $P=.0001$] and vertical activity [$F(9,162)=5.5085$, $P<.0001$], there was no significant Day × Age interaction for either measure. These two measures remained higher for the young rats throughout habituation. Movement speed increased for both age groups during habituation [$F(9,162)=3.8278$, $P<.0005$].

3.2. Vehicle values

When distance traveled was summed across the 60-min session, the old rats traveled 56% less than the young rats [$t(18)=6.622$, $P<.0001$] (see Table 1). Likewise, total vertical activity was 80% lower in the aged group than in the young group [$t(18)=7.483$, $P<.0001$]. Average move-

Table 1
Average locomotor activity measures for vehicle sessions in 6- and 24-month-old F344 rats

	6 months	24 months
Total distance (cm)*	**2053** (±154)	**882** (±62)
Average movement speed (cm/s)	**7.9** (±0.2)	**7.6** (±0.2)
Total vertical activity (number)*	**163** (±16)	**30** (±5)

Shown are the mean values (bold type) and standard errors of means (in parentheses).

* Significant age difference, $P<.0001$.

ment speed was only 4% slower in the aged animals, a difference that did not reach significance.

3.3. Young rats

To illustrate relative effects in young versus old rats, drug effects for each age group are depicted in Figs. 2 (fluoxetine), 3 (sertraline), and 4 (nomifensine) as percentages of vehicle baseline for each dose (data analyses were conducted with raw data). Fluoxetine significantly diminished total distance traveled [$F(3,27)=4.595$, $P=.01$], average movement speed [$F(3,27)=25.466$, $P<.001$], and vertical activity [$F(3,27)=6.328$, $P<.005$] in the young rats. Post hoc contrasts confirmed that fluoxetine's motor-diminishing

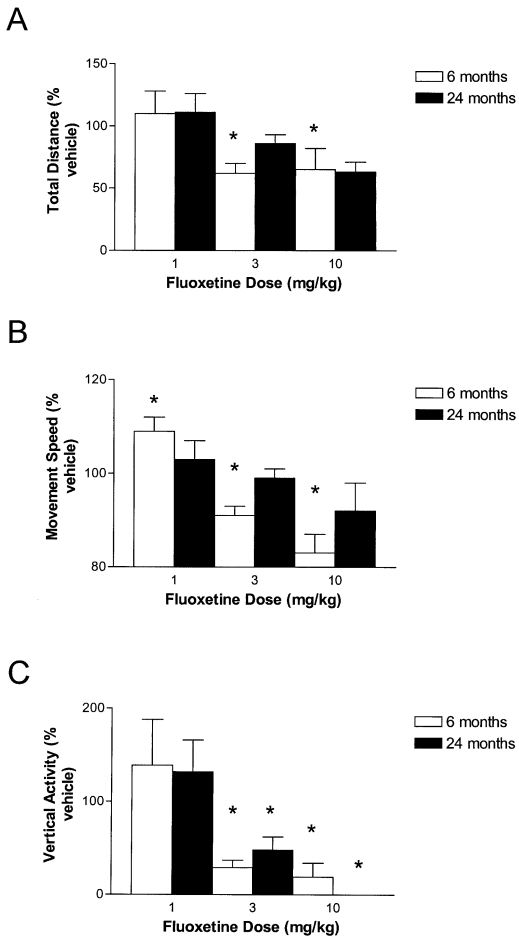

Fig. 2. Effects of fluoxetine on locomotor activity measures in young versus aged F344 rats. * Significant difference from vehicle as determined by post hoc contrast following a significant omnibus main effect for dose ($P<.05$). (A) Fluoxetine significantly reduced total distance traveled in young rats at the 3- and 10-mg/kg doses. Total distance traveled was not significantly affected by fluoxetine in the old rats. (B) In the young animals, fluoxetine significantly increased average movement speed at the 1-mg/kg dose, but diminished the measure at the 3- and 10-mg/kg doses. Average movement speed was not significantly affected by fluoxetine in the old rats. (C) Fluoxetine diminished vertical activity in the young rats at the 3- and 10-mg/kg doses. In the old rats, fluoxetine diminished vertical activity at the 3- and 10-mg/kg doses.

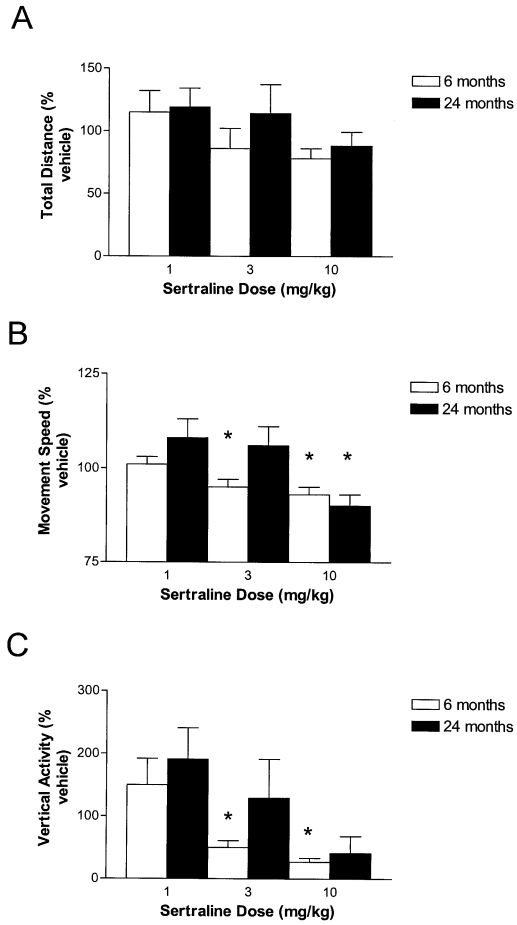

Fig. 3. Effects of sertraline on locomotor activity measures in young versus aged F344 rats. * Significant difference from vehicle as determined by post hoc contrast following a significant omnibus main effect for dose ($P<.05$). (A) Sertraline produced no significant effects on total distance traveled in either group. (B) In the young animals, sertraline significantly diminished average movement speed at the 3- and 10-mg/kg doses. Average movement speed was significantly diminished by sertraline at the 10-mg/kg dose in the old rats. (C) Sertraline diminished vertical activity in the young rats at the 3- and 10-mg/kg doses. Although it produced a significant overall effect on vertical activity in the old rats, sertraline's effect were not significant at any of the individual doses.

effects for all three measures were significant at the 3- and 10-mg/kg doses for the young rats (all P's $<.05$) (see Fig. 1). While fluoxetine produced motor attenuation at the 3- and 10-mg/kg doses, post hoc contrasts revealed that it produced a significant increase in movement speed in the young group at 1 mg/kg ($P<.05$). Unlike fluoxetine, sertraline did not significantly affect total distance traveled in the young rats. Sertraline did, however, significantly diminish average movement speed [$F(3,27)=3.879$, $P<.05$] and vertical activity [$F(3,27)=9.559$, $P<.0005$] (see Fig. 3). Post hoc contrasts confirmed that sertraline's effects on these two measures were significant at both the 3- and 10-mg/kg doses in the young rats (all P's $<.05$). Unlike fluoxetine and sertraline, nomifensine produced robust increases in total distance traveled [$F(3,27)=30.491$, $P<.001$], average movement speed [$F(3,27)=10.112$, $P<.001$], and vertical

activity [$F(3,27) = 1.940$, $P < .0001$] in the young animals (see Fig. 4). Post hoc contrasts confirmed that these increases produced by nomifensine on the three measures were significant at every dose (all P's $< .05$).

3.4. Aged rats

In the aged rats, fluoxetine's motor-diminishing effects were limited to a robust attenuation of vertical activity [$F(3,21) = 8.060$, $P < .001$] (see Fig. 2). This effect was significant at the 3- and 10-mg/kg doses as determined by post hoc contrasts (both P's $< .05$). Sertraline produced a significant decrease in average movement speed in the old rats [$F(3,24) = 5.407$, $P < .01$], an effect that was significant at the 10-mg/kg dose as determined by post hoc contrast ($P < .05$) (see Fig. 3). There was also a significant overall effect of sertraline on vertical activity [$F(3,24) = 3.142$, $P < .05$]. Unlike fluoxetine, however, sertraline's effect on vertical activity was not significant at any individual dose. Indeed, post hoc contrasts between each dose and vehicle suggest that sertraline's *augmentation* of vertical activity at 1 mg/kg ($P = .07$) probably contributed more to the significant overall effect on the measure than the effect at 10 mg/kg ($P = .20$). Neither fluoxetine nor sertraline significantly affected total distance traveled in the aged rats. As it did in the young rats, nomifensine produced robust increases in total distance traveled [$F(3,21) = 62.04$, $P < .001$] and vertical activity [$F(3,21) = 6.513$, $P < .005$] in the old rats. Post hoc contrasts confirmed that nomifensine's effects on these measures were significant at each dose administered (all P's $< .05$). Nomifensine also significantly increased average movement speed in the old rats [$F(3,21) = 10.112$, $P < .001$]. Unlike the young rats, however, nomifensine's significant effect on movement speed was limited to the 1-mg/kg dose ($P < .05$).

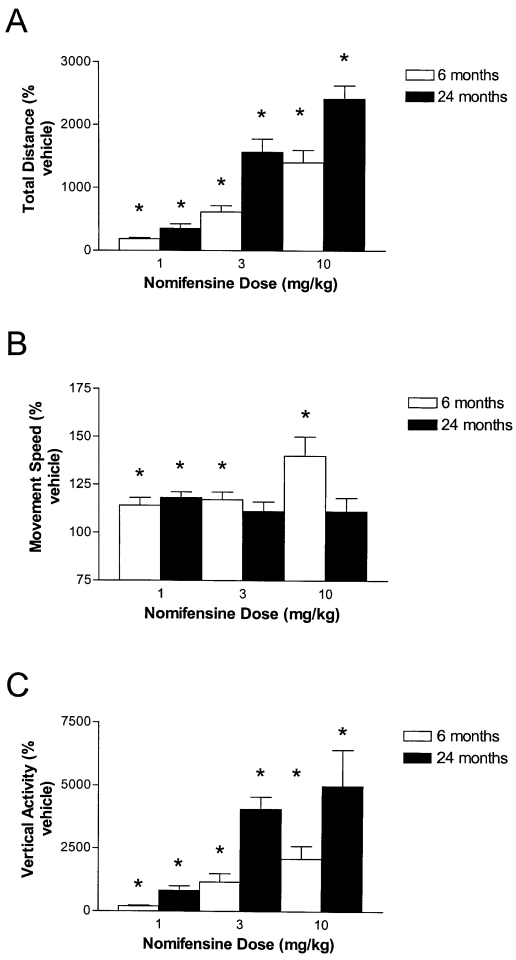

Fig. 4. Effects of nomifensine on locomotor activity measures in young versus aged F344 rats. * Significant difference from vehicle as determined by post hoc contrast following a significant omnibus main effect for dose ($P < .05$). (A) Nomifensine produced robust increases in total distance traveled in both young and old rats at each dose. (B) Nomifensine increased movement speed at all doses in the young rats, but in the old rats, nomifensine's effect was only significant at the 1-mg/kg dose. (C) Nomifensine produced robust increases in vertical activity in both young and old rats at each dose.

4. Discussion

In the present study, the acute effects of the antidepressant drugs fluoxetine, sertraline, and nomifensine on spontaneous locomotor activity in young versus aged F344 rats were assessed. Following habituation, predrug analyses revealed that the total distance traveled and vertical activity exhibited by the aged rats during the 60-min sessions were substantially impaired compared to the young rats, while average movement speed did not differ between the two age groups. Fluoxetine significantly diminished all three measures in the young animals while sertraline diminished movement speed and vertical activity in this group (these effects were generally observed at the 3- and 10-mg/kg doses for both drugs). In the motor-impaired aged rats, fluoxetine produced further attenuations of vertical activity but did not affect total distance traveled or movement speed. Sertraline's effects in the aged group were limited to a significant effect on vertical activity that may have resulted from its augmentation of the measure at the lower doses. Nomifensine significantly increased total distance traveled and vertical activity at each dose in both groups. Nomifensine produced a dose-dependent increase in movement speed in the young rats, but only increased the measure at the 1-mg/kg dose in the old rats. These results suggest that the acute motor attenuating effects of fluoxetine and sertraline decrease with age.

While previous studies using young rats have reported either decreased or no changes in locomotor activity following acute doses of sertraline and fluoxetine (Koe et al., 1983; Maj et al., 1996; Sills et al., 1999), there have been no reports of the effects of these drugs on spontaneous motor activity in aged animals. In young animals, the acute systemic administration of SSRIs has been reported to

attenuate DA function in the basal ganglia (Clark et al., 1996; Dewey et al., 1995; Ichikawa and Meltzer, 1995) and augment extracellular DA levels in the prefrontal cortex (Gobert et al., 1997; Tanda et al., 1995), suggesting that these drugs may exacerbate age-related motor impairment. However, with the exception of vertical activity (which was diminished to a greater extent in the aged rats than in the young rats), fluoxetine's effects were greater in the young rats than in the old rats. Likewise, sertraline, which diminished movement speed and vertical activity in the young rats, produced no significant motor attenuations in the old rats. These results suggest that the acute effects of these drugs may be less motorically impairing in the elderly than in the young.

Upon examination of the baseline values for total distance traveled and vertical activity in the aged group, it could be argued that a "floor effect" prevented further drug-related decreases in these measures. However, the facts that (a) vertical activity was essentially absent in the aged rats following the high dose of fluoxetine and (b) total distance traveled was appreciably lower in the aged rats for the high dose of fluoxetine compared to the high dose of sertraline, suggest otherwise. With the exception of the effect of fluoxetine on vertical activity in the aged animals, the lesser effect of the drugs in the aged animals may reflect age-related alterations in the interaction between central 5-HT and DA systems. For example, age-related decreases in striatal 5-HT content and increases in 5-HIAA (a 5-HT metabolite) and the ratio of 5-HIAA to 5-HT (both reflecting higher 5-HT turnover) in the striatum have been previously reported (Godefroy et al., 1989; Gozlan et al., 1990; Woods and Druse, 1996). Because some studies have demonstrated an inhibitory effect of 5-HT or 5-HT agonists on nigrostriatal or mesolimbic DA function (Ennis et al., 1981; Kelland et al., 1990, 1993; Meltzer et al., 1979; Prisco and Exposito, 1995; Prisco et al., 1994), diminished 5-HT function in the aged rats may have resulted in diminished attenuation of DA function. Further studies are necessary, however, to test this hypothesis.

Although the acute effects of SSRIs at the doses administered here may be behavioral suppressing, there is previous evidence that repeated administration with these agents may yield different results. For example, it has been demonstrated that while acute fluoxetine has no effect on the hypolocomotor effect of mCPP, chronic administration of the drug attenuates mCPP's effect (Kennett et al., 1994). There is evidence that the behavioral stimulating effects of chronic fluoxetine may be mediated via dopaminergic mechanisms. For example, it has been reported that chronic — but not acute — fluoxetine has a sensitizing effect on quinpirole-induced hypermotility in rats (Collu et al., 1997). These authors cited the demonstration that chronic fluoxetine increases rats' ability to discriminate cocaine (Simon and Appel, 1995) as evidence for the DA sensitizing effect of chronic fluoxetine. A differential effect of SSRIs as a function of repeated administration would certainly be consistent with the drugs' well-known therapeutic lag (Goodnick and Goldstein, 1998). Indeed, in the case of sertraline, the drug's relatively potent DA transporter-blocking properties may have a synergistic effect upon motor activity when combined with a potential fluoxetine-like sensitization of DA function resulting from chronic administration.

The fact that nomifensine increased locomotor activity was expected based on previous reports of similar findings (Hebert and Gerhardt, 1998; Maj et al., 1996; Marshall and Altar, 1986). In the present study, the increases in total distance traveled and vertical activity from vehicle values were greater for the older animals than for the young animals. In a previous study from this laboratory, nomifensine (at 5.0 mg/kg) also increased total distance traveled in 24-month-old F344 rats, but only to the level of their vehicle-treated 6-month-old counterparts (Hebert and Gerhardt, 1998). Others have reported that aged rats exhibit diminished behavioral sensitivity to D-amphetamine (Warenycia and McKenzie, 1989; Yurek et al., 1998). While age-related attenuations in neurochemical responses to D-amphetamine have been consistently reported (Gerhardt and Maloney, 1999; Kametani et al., 1995; Yurek et al., 1998), reports of age-related differences in neurochemical responses to nomifensine have been mixed, with some studies reporting differences as a function of age (Friedemann, 1992; Friedemann and Gerhardt, 1992; Hebert and Gerhardt, 1999) and others reporting no age-related differences (Santiago et al., 1993; Stamford, 1989). The reason for the discrepancies in nomifensine's behavioral effects between this and our previous study is unclear, but may be related to several procedural differences between these studies. For example, in the present study, rats were placed in the monitors 30 min after their injections instead of immediately as in the previous study. This delay may have diminished age-related differences in DA responsiveness to the mild stress produced by handling and injection (Abercrombie et al., 1989; Barrot et al., 2000; Cizza et al., 1995; Johnson and Glick, 1994). Indeed, this procedural difference may account for the substantial differences in basal habituated locomotor activity between the aged rats in this study (total distance traveled <1000 cm/h) versus that observed in previous studies (total distance traveled ca. 2000 cm/h) (Hebert and Gerhardt, 1998, 1999). In addition, in the present study, habituation was completed within 2 weeks, while in the previous study, habituation occurred over the course of over 2 months. Other differences, such as in handling or animal facilities may have also contributed.

Although nomifensine's activating effects on locomotor activity measures have been reported previously, this is the first study to report age-related differences in the drug's effect on movement speed. Specifically, nomifensine's effects on movement speed were greater in the young rats than in the aged rats. While the total distance traveled and vertical activity measures are constrained by the duration of the session, the only limitations on average movement speed

are the resolution of the activity monitors and the movement capacity of the animals. The fact that the young rats exhibited similar vehicle values for movement speed as the old rats but moved faster following the high dose of nomifensine suggests that the capacity for increased movement speed was limited in the aged rats. This suggestion is supported by previous findings demonstrating diminished movement speed in aged rats (Hebert and Gerhardt, 1998) and humans (Imms and Edholm, 1981; Murray et al., 1969). The fact that we failed to detect baseline differences in movement speed between the two groups may also be related to the procedural differences addressed above.

Three measures of locomotor activity were assessed in the current study. Under vehicle conditions, of the variables that differed between the two age groups, vertical activity differed more than total distance traveled. Vertical activity was also the variable most affected by the motor-attenuating effects of fluoxetine in the aged animals. These findings suggest that vertical activity may be a more sensitive measure of spontaneous motor activity than total distance traveled. Because rearing arguably involves more muscle strength and balance than movement in the horizontal plane, this is not surprising since previous studies have demonstrated diminished muscle strength and balance in elderly rats and humans (Bowenkamp et al., 2000; Kauffmann, 1994; Luff, 1998).

Because of the progressive aging of the population and the fact that depression is the predominant psychiatric affliction in the elderly (Gareri et al., 2000), the use of antidepressant drugs in the aged population is expected to increase. Moreover, if repeated exposure to SSRIs causes an upregulation in DA function as preliminary evidence suggests, its use in age-related akinesia may be warranted. Consequently, the tendency for these drugs to produce transient motor side effects during the pretherapeutic period will be an increasingly important issue, especially since their presence may affect compliance. The current study suggests that the motor-attenuating effects of SSRIs may be less in the elderly than in the young. Further characterization of age-related differences in the motor effects of these drugs in the laboratory under repeated dosing treatments is necessary to influence their use in the clinic.

Acknowledgments

This work was supported by USPHS Grant Nos. AG06434, AG13494, NS39787, and a Level II Research Scientist Award (MH01245) to G.A.G.

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